Effects of Ouabain on Myocardial Oxygen Supply and Demand in Patients with Chronic Coronary Artery Disease

A HEMODYNAMIC, VOLUMETRIC, AND METABOLIC STUDY IN PATIENTS WITHOUT HEART FAILURE

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ABSTRACT The effects of digitalis glycosides on myocardial oxygen supply and demand are of particular interest in the presence of obstructive coronary artery disease, but have not been measured previously in man. We assessed the effects of ouabain (0.015 mg/kg body weight) on hemodynamic, volumetric, and metabolic parameters in 11 patients with severe chronic coronary artery disease without clinical congestive heart failure. Because the protocol was long and involved interventions which might affect the determinations, we also studied nine patients using an identical protocol except that ouabain administration was omitted.

Left ventricular end-diastolic pressure and left ventricular end-diastolic volume fell in each patient given ouabain, even though they were initially elevated in only two patients. Left ventricular end-diastolic pressure fell from 11.5±1.4 (mean±SE) to 5.6±0.9 mm Hg ($P <$ 0.001) and left ventricular end-diastolic volume fell from 100±17 to 82±12 ml/m^2 ($P < 0.01$) 1 h after ouabain infusion was completed. The maximum velocity of contractile element shortening increased from 1.68± 0.11 ml/s to 2.18±0.21 muscle-lengths/s ($P < 0.05$) and is consistent with an increase in contractility. No significant change in these parameters occurred in the control patients.

No significant change in myocardial oxygen consumption occurred after ouabain administration but this may be related to a greater decrease in mean arterial pressure in the ouabain patients than in the control patients.

We conclude that in patients with chronic coronary artery disease who are not in clinical congestive heart failure left ventricular end-diastolic volume falls after ouabain administration even when it is initially normal. Though this fall would be associated with a decrease in wall tension, and, therefore, of myocardial oxygen consumption, it may not be of sufficient magnitude to prevent a net increase in myocardial oxygen consumption. Nevertheless, compensatory mechanisms prevent a deterioration of resting myocardial metabolism.

INTRODUCTION

The effects of digitalis glycosides on myocardial oxygen consumption (MVO_2)[1] and the determinants of MVO_2 have been studied extensively in animals. It has been previously demonstrated that MVO_2 increased when acetyl strophanthidin was given to nonfailing canine preparations (1). However, no change in MVO_2 occurred in a heart failure preparation. Ventricular volume, and therefore wall tension, decreased more in failing hearts than in the nonfailing hearts and as a result, the increase in MVO_2 caused by the enhanced contractile state was completely balanced.

The study of digitalis in patients with coronary artery disease without congestive heart failure is clinically

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[1] *Abbreviations used in this paper:* (A-CV)O_2, arterial-coronary venous oxygen difference; ML/s, muscle-lengths/second; MVO_2, myocardial oxygen consumption; Vmax, maximum rate of contractile element shortening.

relevant. Left ventricular dysfunction frequently occurs without clinical heart failure and digitalis improves ventricular function in such patients (2–6). The salutary effects of digitalis may be translated into improved tissue perfusion or into cardiac reserve (2). Digitalis is commonly given to provide cardiac reserve to patients with a history of recurrent heart failure who are in a compensated state most of the time. In addition, it is used for the therapy of cardiac arrhythmias and as a prophylactic measure to cardiac and noncardiac surgery. However, these factors must be considered in relation to its effects on myocardial oxygen supply and demand because ouabain may impose an undesirable metabolic cost to the myocardium simultaneous with the improved performance. Coronary artery disease without heart failure may represent the clinical state in which the metabolic effects are least favorable.

This study of 11 patients with chronic coronary artery disease without congestive heart failure examines the effect of ouabain on myocardial oxygen needs and supply and relates them to concurrent changes in hemodynamic and volumetric determinants.

METHODS

Patients with a clinical history of angina pectoris and coronary arteriographic evidence of coronary artery disease who were undergoing diagnostic cardiac catheterization were studied. Patients with unstable angina or recent myocardial infarction were excluded. Informed consent was obtained from each patient. There were nine men and two women whose age ranged from 34 to 64 yr. 10 patients were in New York Heart Association (7). Functional Class III because of angina and one patient was Functional Class II. 6 of 11 patients gave a history of prior myocardial infarction. Electrocardiograms showed evidence of prior myocardial infarction in five patients. Episodes of clinical congestive heart failure had been documented in three patients. At the time of the study the left ventricular end-diastolic pressures in these three individuals were 9, 11, and 14 mm Hg. Six patients had received digitalis glycosides in the past but in each instance the drug had been discontinued at least 3 wk before the study without clinical evidence of deterioration of cardiac function. All patients were in sinus rhythm. Chest x rays were normal except in one patient in whom mild cardiomegaly was present. A fourth heart sound was present in five patients; no patient had a protodiastolic gallop. Two patients had mild systemic hypertension that was well controlled with thiazides. However, no diuretic had been administered within 24 h of the study.

Coronary arteriograms performed on the day before or after the study demonstrated significant coronary artery disease of one or more of the three major coronary arteries (left anterior descending, left circumflex, or right coronary arteries) in each patient. Three vessels were significantly narrowed in four patients, two vessels in four patients, and one vessel in three patients. In addition three of the patients also had significant left main coronary artery disease. A vessel was considered significantly narrowed when luminal diameter was reduced 50% (75% cross sectional narrowing).

To assure that the changes observed were the effects of ouabain and not simply related to the duration of the procedure or the late effects of contrast material (8–11) a group of 10 patients was studied by an identical protocol except that saline was given instead of ouabain. Five of these control patients had coronary artery disease, three valvular heart disease, and one an ostium secundum atrial septal defect.

The study evaluated changes in hemodynamics, ventricular volumes, and myocardial metabolism in both the ouabain and control groups.

Hemodynamic measurements. Brachial artery and left ventricular pressures were recorded using fluid-filled catheter systems, Statham P23Db transducers (Statham Instrument Div., Oxnard, Calif.), and an Electronics for Medicine DR16 (White Plains, N. Y.) recorder. The first derivative of left ventricular pressure (dp/dt) was obtained using an RC differentiator (12). The limitations and characteristics of such a system are known (12–14). The maximum rate of contractile element shortening (Vmax), was determined by an abbreviated method described and validated previously (15). The heart rate was determined from the electrocardiogram. Cardiac output was determined by the cardio-green indicator dilution technique using paired 5-mg injection into the left ventricle and sampling from the brachial artery through a Waters densitometer (Waters Associates, Inc., Milford, Mass.). After each determination of cardiac output the blood was reinfused. At the end of the procedure calibration of the densitometer was performed using the patients blood.

Volumetric measurements. Left ventricular cineangiography was performed in the right anterior oblique projection using meglumine and sodium diatrizoates (Renografin-76, E. R. Squibb and Sons, New York) and filming at 60 frames/s. The extent of x-ray magnification was determined by filming a lead impregnated ruler at the height of the cardiac apex. Ventricular volumes were determined by standard techniques from traced silhouettes of end-diastolic and end-systolic frames (16). The same observer made each volumetric assessment. We have previously shown that the variation between two such assessments of the same angiogram when performed by the same observer is less than 5% (17). End-diastole was determined using a cine-event marker and the electrocardiogram. End-systole was identified as the smallest subsequent silhouette. The ejection fraction was calculated as the quotient of the angiographically determined stroke volume and end-diastolic volume. Extra-systolic and postextrasystolic beats and inadequately opacified angiograms were excluded from analysis. When possible the average of 2 or 3 beats was used but in some instances only one beat from an angiogram was satisfactory for analysis. Volumetric data is included for only seven of the patients given ouabain and six of the controls because one or both angiograms was unsuitable for analysis in the remaining patients.

Metabolic measurements. Coronary blood flow was measured by the exponential rate of myocardial clearance of Xenon 133 after a bolus injection of 100 μCi of the isotope into the left ventricle. Simultaneous sampling of blood from the coronary sinus and brachial artery catheters was performed using a manifold beginning 1 min after injection and continuing until five sequential, 15 s, 1.5 ml-samples were collected from each catheter (18). Flow per unit weight was calculated from a standard formula (19).

Simultaneous brachial artery and coronary sinus samples were also obtained for PO_2, PH, hemoglobin, and lactate

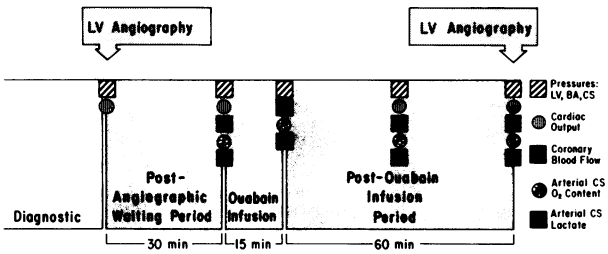

FIGURE 1 A flow diagram of the study. See text for description.

concentration. Oxygen content was determined from PO_2, PH, and hemoglobin using a Severinghaus nomogram (20) and assuming a normal hemoglobin-oxygen dissociation curve. Serum lactate was measured by a modification of the enzymatic method of Horn and Bruns (21, 22). Myocardial oxygen consumption was calculated as the product of coronary blood flow and arterial-coronary venous oxygen difference ({A-CV}O_2 difference). Lactate extraction was calculated as the quotient of the arterial-venous difference and the arterial concentration.

Study plan. The study was divided into several phases (Fig. 1). After completion of the diagnostic phase during which no contrast material was used, hemodynamic parameters were measured and the initial left ventricular angiogram obtained. ½ h was allowed to elapse to assure dissipation of the acute effect of contrast material (8–10). Hemodynamic parameters were again measured to test whether the hemodynamic state had returned to base-line levels. Base-line metabolic parameters were measured and a 15-min infusion of ouabain (0.015 mg/kg body weight) was given. The average dose of ouabain was 1.1 mg. After completion of the ouabain infusion and 30 and 60 min after completion of the infusion, hemodynamic and metabolic parameters were measured. A repeat left ventricular angiogram was performed as the final measurement 1 h after completion of the infusion, a time when the inotropic effect is maximal. The same time sequence was followed in the control group of patients except that ouabain was not given.

RESULTS

The results are summarized in Table I.

Hemodynamic measurements. Heart rate, cardiac output, brachial artery pressure, and left ventricular end-diastolic pressure before and ½ h after the first angiogram are shown in Table II. No statistically significant change occurred in any of these parameters. This data indicates a return to the resting hemodynamic state at the time the ouabain infusion was initiated.

After the administration of ouabain no significant change occurred in heart rate or cardiac output at any time. Left ventricular end-diastolic pressure was initially normal (less than 12 mm Hg) in all but two patients and decreased further in each patient (Fig. 2). At the conclusion of the 15-min ouabain infusion left ventricular end-diastolic pressure had already fallen from 11.5± 1.4 mm Hg (mean±SEM) to 8.6±1 mm Hg ($P < 0.01$). A progressive decrease in left ventricular end-diastolic pressure occurred until 1 h after the conclusion of the infusion when it was 5.6±0.9 mm Hg ($P < 0.001$). In the control group left ventricular end-diastolic pressure fell from 9.9±2.2 to 8.9±1.9 mm Hg ($P < 0.3$). The fall in end-diastolic pressure in the ouabain treated group was significantly different from the fall seen in the controls ($P < 0.001$). Mean brachial artery pressure fell from 102±6 mm Hg to 91±4 mm Hg 1 h after completion of the infusion ($P < 0.05$). In the controls mean arterial pressure fell from 97±3 to 94±3 mm Hg ($P < 0.2$). The extent of fall in the ouabain treated patients was not different than the extent of fall in the controls ($P < 0.3$)

Vmax increased from 1.68±0.10 ML/s to 1.96±0.18 ML/s by the end of the infusion ($P < 0.05$) and continued to increase to 2.18±0.21 ml/s 1 h after the conclusion of the ouabain infusion. In six patients not given ouabain Vmax changed from 1.54±0.17 to 1.62±0.06 ml/s at the conclusion of the procedure ($P < 0.6$).

Volumetric measurements. The initial end-diastolic volume was normal (85±25: mean±2SD) (23) in five of seven patients in whom two satisfactory angiograms were obtained. In each patient both the end-diastolic and end-systolic volume were smaller 1 h after completion of the ouabain infusion. The initial end-diastolic volume for the seven patients was 100±15 ml/m² and fell to 82±12 ml/m² ($P < 0.01$). In the control group left ventricular end-diastolic volume fell from 88±12 ml/m² to 83±12 ml/m² ($P < 0.8$). The change in left ventricular end-diastolic volume for the ouabain group (18%) was statistically different than the change in end-diastolic volume for the controls (8%) ($P < 0.01$).

Similarly, end-systolic volumes fell from 50.3±11.4 to 35±11.8 ml/m² ($P < 0.005$) in the ouabain treated patients and from 44.3±9.5 to 41±9.5 ml/m² in the control group ($P < 0.2$).

The ejection fraction rose in five of seven patients, was unchanged in one, and fell in another. The patient in whom the ejection fraction fell had a large area of apical dyskinesis and the fall in end-diastolic volume was proportionally larger than the fall in end-systolic volume. Mean ejection fraction for the group rose from 0.57±0.05 to 0.63±0.06 ($P < 0.2$). In the control group ejection fraction was 0.52±0.05 initially and rose to 0.54±0.07 at the end of the procedure ($P < 0.7$).

Areas of akinesis and dyskinesis which were present in three patients did not change after ouabain. No hypokinetic segment became akinetic or dyskinetic. The assessment of changes in hypokinetic and normal wall segments is more difficult than in akinetic or dyskinetic segments. Quantitation of segmental wall motion is possible and has been used to differentiate normal from abnormal segments but standards which allow estimation of the significance of small changes of normally moving segments within the normal range or hypokinetic seg-

TABLE I

Data Summary before and after Ouabain

Parameter	Time	Ouabain			Control		
		n	Mean±SE	*P*	*n*	Mean±SE	*P*
	min						
Hemodynamic							
HR, *beats/min*	Preinfusion	11	75±3	—	8	87±7	—
	0	8	73±4	<0.1			
	30	11	75±4	<0.9	8	87±7	<0.5
	60	11	77±4	<0.4	8	87±8	<0.3
MAP, *mm Hg*	Preinfusion	11	102±6	—	9	97±3	—
	0	11	102±5	<0.9			
	30	11	92±4	<0.02	9	96±4	<0.7
	60	11	91±4	<0.05	9	94±3	<0.2
CO, *l/min per m²*	Preinfusion	11	2.7±0.3	<0.6	9	2.6±0.6	<0.6
	0	11	2.6±0.4	<0.6			
	30	11	2.6±0.4	<0.6	9	2.5±0.5	<0.6
	60	11	2.5±0.5	<0.7	9	2.5±0.5	<0.7
LVEDP, *mm Hg*	Preinfusion	11	11.5±1.4	—	9	9.9±2.2	—
	0	11	8.6±1.0	<0.01			
	30	11	6.7±0.8	<0.01	9	9.7±2.3	<0.8
	60	11	5.6±0.9	<0.001	9	8.9±1.9	<0.3
V_{max}, *ml/s*	Preinfusion	7	1.68±0.11	—	6	1.54±0.17	—
	0	7	1.96±0.18	<0.05			
	30	7	2.09±0.18	<0.05	6	1.49±0.13	<0.6
	60	7	2.18±0.21	<0.05	6	1.63±0.07	<0.6
Volumetric							
EDV, *ml/m²*	Preinfusion	7	100±17	—	6	88±12	—
	60	7	82±12	<0.01	6	83±12	<0.8
ESV, *ml/m²*	Preinfusion	7	50.3±11.4		6	44.3±9.5	—
	60	7	35.0±11.8	<0.005	6	41.0±9.5	<0.2
EF	Preinfusion	7	57±5	—	6	52±5	—
	60	7	63±6	<0.2	6	54±7	<0.7
Metabolic							
CBF, *ml/min per 100 g*	Preinfusion	10	117±17	—	4	146±0.22	—
	0	10	119±13	<0.9			
	30	10	114±11	<0.8	4	155±23	<0.4
	60	9	110±12	<0.2	4	131±26	<0.5
(A-CV)O_2 difference, *ml O_2/ml blood*	Preinfusion	10	11.31±0.34	—	4	11.09±1.0	—
	0	10	12.22±0.56	<0.05			
	30	10	11.79±0.42	<0.3	4	10.94±0.8	<0.5
	60	10	11.84±0.34	<0.3	4	10.21±0.5	<0.05
MVO_2, *ml O_2/min per 100 g*	Preinfusion	9	13.62±2.4	—	4	14.89±1.1	—
	0	9	14.22±1.9	<0.6			
	30		12.97±1.3	<0.7	4	15.20±1.4	<0.7
	60	8	12.56±1.8	<0.4	4	11.97±1.8	<0.2
Lactate, *% Extraction*	Preinfusion	11	19.7±4	—			
	0	9	15.8±4	<0.2			
	30	9	15.8±5	<0.3			
	60	11	15.6±5	<0.4			

Abbreviations: HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; V_{max}, the maximum velocity of contractile element shortening; ML/sec, muscle lengths/second; EDV, end diastolic volume; ESV, end-systolic volume; EF, ejection fraction; CBF, coronary blood flow; MVO_2, myocardial oxygen consumption.

All *P* values refer to the significance of changes from the preinfusion period. Zero time occurred at the conclusion of the 15-min ouabain or saline infusion.

TABLE II

Hemodynamic Measurements before and ½ h after Angiography

	Preangio	Postangio	P
HR, *beats/min*	78±15	79±13	>0.7
MAP, *mm Hg*	97.5±18.4	100.4±16.9	>0.3
CO, *l/min/m²*	2.6±0.4	2.7±0.4	>0.6
LVEDP, *mm Hg*	10.3±5.0	10.5±4.8	>0.3

Results are mean±SE.

ments within the hypokinetic range (17, 24) are not available. In addition the effects of volume changes on the reliability of these methods have not been tested.

Metabolic measurements. Minimal changes occurred in coronary blood flow, (A-CV) O_2 difference, myocardial oxygen consumption, and lactate extraction in the ouabain group and none of the changes were statistically significant. In the control group coronary blood flow, (A-CV) O_2 difference, and myocardial oxygen consumption all decreased but only the change in oxygen extraction was statistically significant ($P < 0.05$).

Though there was no change in myocardial oxygen consumption and coronary blood flow for the ouabain group as a whole there was considerable variation in changes observed in individual patients. These changes ranged from a 31% decrease to a 42% increase in myocardial oxygen consumption and from a 32% decrease to an 18% increase in coronary blood flow. Changes in these two parameters were found to correlate highly with changes in mean arterial pressure, (r = 0.88, and 0.84, respectively). The relationship of the changes in MVO_2 to the changes in mean arterial pressure is described graphically and by formula in Fig. 3. This high degree of correlation suggests that changes in mean arterial pressure occurring during the study were a major determinant of changes in myocardial oxygen consumption.

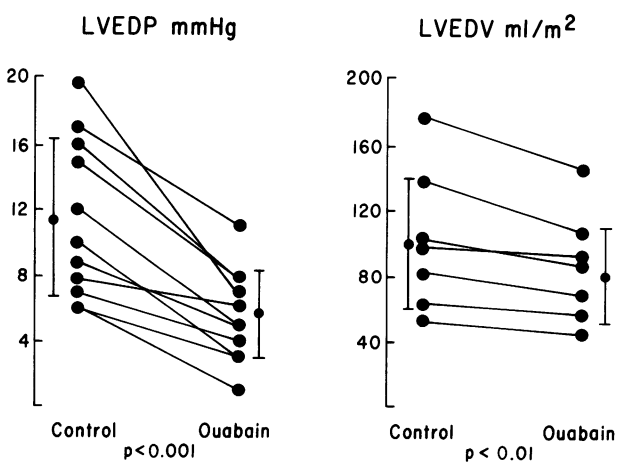

FIGURE 2 Changes in end-diastolic volume and pressure. After ouabain administration end-diastolic pressure and volume fell in each patient.

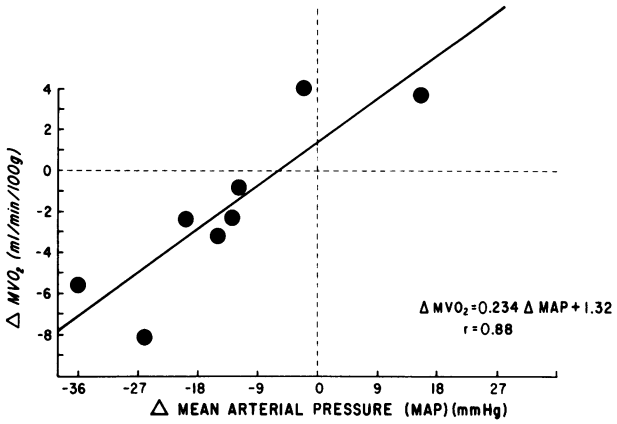

FIGURE 3 The relationship of MVO_2 to MAP. If MAP had not fallen a 1.3±1.0 ml/min per 100 g increase in MVO_2 would have occurred in the ouabain patients shown by the circles.

Coronary blood flow, (A-CV) O_2 difference, and MVO_2 were determined in four of the controls. The mean arterial pressure varied widely in the control group as it did in the ouabain group, but in the four patients in whom coronary blood flow and MVO_2 were assessed there was an increase of only 1.0±0.7 mm Hg (range — 3–7 mm Hg). The decrease in MVO_2 in these four control patients was 3.0±1.1 ml/min per 100 g and the decrease in coronary blood flow was 24±8 ml/min per 100 g. Since there was essentially no change in mean arterial pressure in these four patients, the decrease in MVO_2 observed must be attributed to other nonspecific effects of the procedure such as the slow volume depletion after contract injection (10).

The (A-CV) O_2 difference increased from 11.3±0.3 ml to 12.1±0.6 ml ($P < 0.05$) by the conclusion of the infusion. Then as arterial pressure began to fall in 9 of the 11 patients, the (A-CV) O_2 difference also decreased to 11.8±0.34 1 h after the infusion ($P < 0.3$). At the end of 1 h the (A-CV) O_2 difference had increased from the control value in all but three patients. The (A-CV) O_2 difference increased in all patients in whom the arterial pressure either increased or fell less than 12 mm. Hg.

In the control patients by contrast, the (A-CV) O_2 difference fell from 11.1±1.0 ml to 10.2±0.5 ml ($P < 0.005$). The difference between the two groups was not significant possibly because of the effect of falling arterial pressure in the ouabain group.

Lactate extraction remained within the normal range (greater than 8% extraction) at all times (25). It fell from 19.7±4% to 15.6±5% at the end of 1 h ($P < 0.4$).

No chest pain or electrocardiographic abnormalities of ischemia occurred in any patient.

DISCUSSION

The usefulness of digitalis may be examined by considering its electrophysiologic and hemodynamic effects and its metabolic cost. This study is directed primarily to the metabolic cost; specifically the change in oxygen supply and demand. We also performed hemodynamic and volumetric measurements because of the relationship of these factors to myocardial oxygen supply and demand. Measurement of hemodynamic and volumetric parameters further defines the patient population. It is important to identify as closely as possible the patients under study because the results obtained in one clinical or hemodynamic setting may not apply to a different setting.

The salutary effects of digitalis on left ventricular systolic pump function and contractility in the nonfailing heart have been established (2–4) even though an increase in cardiac output may not result. This effect is not lost in coronary artery disease and has even been demonstrated in patients with acute myocardial infarction (5) and patients convalescing from acute myocardial infarction (6). In our patients the increase in Vmax which occurred despite falls in arterial and end-diastolic pressures without an increase in heart rate is compatible with an increase in contractility (26). Because contractility is a major factor determining MVO_2 (27), an increase in MVO_2 in our patients would be anticipated unless other simultaneous changes prevented its occurrence. Precipitation of angina is a possibility whenever MVO_2 increased but no symptomatic or electrocardiographic evidence of myocardial ischemia developed in any of our patients. No significant decrease in lactate production across the myocardium occurred, suggesting that the increased oxygen demand related to the enhanced inotropic state either did not occur or that the demand was met. A fall in ventricular volume and, thus wall tension could either prevent or diminish the increase in oxygen demand. At least two mechanisms, an increase in coronary blood flow and an increase in oxygen extraction by the myocardium are potentially available to compensate for any increase which might occur.

The effects of ouabain on left ventricular volume had not been determined previously in man but a fall in volume has been assumed because end-diastolic pressure falls. A direct rather than an inferential determination is important because (*1*) the effects of digitalis on compliance are unknown, (*2*) patients with coronary artery disease may be operating on an altered pressure-volume curve, and (*3*) the extent of change in volume with a given change in pressure will vary depending on the portion of the pressure-volume curve on which the patient is operating.

Mean arterial pressure fell 12.0±5.6 mm Hg in the ouabain group and rose 1.0±0.7 in the control group. The equation in Fig. 3 can be used to estimate the change in MVO_2 if mean arterial pressure had not changed. The point where the regression line intercepts the line denoting no change in mean arterial pressure and the confidence limits of that point can be calculated using standard formulae (28). The intercept occurs at 1.3± 1.0 ml/min per 100 g. This value can then be compared with the value for MVO_2 obtained in the controls in whom a negligible change in mean arterial pressure occurred. The difference between these two values for MVO_2 (1.3±1.0 and -3.0±1.1 ml/min per 100 g) is statistically significant ($P < 0.02$). Similar calculations can be performed for coronary blood flow and a statistically significant difference demonstrated between the two groups ($P < 0.05$). This suggests that an increase in MVO_2 was masked by the changes in mean arterial pressure attending the procedure.

The reason for the fall in arterial pressure in these two groups of patients probably relates to multiple factors in the procedures such as the late effects of contrast medium. A gradual slow fall in plasma volume is known to continue for several hours after contrast injection (11). Identification of all factors responsible for the fall in arterial pressure is probably not possible nor is it crucial to answering the questions posed in this study because a control group of patients was also studied. Regardless of the cause of the fall in arterial pressure, however, it must be carefully considered in the interpretation of the results because arterial pressure is an important determinant of coronary blood flow and MVO_2 (27, 29). In the clinical setting a fall in mean arterial pressure would not be anticipated after ouabain administration. Therefore, it seems most reasonable to compare changes in coronary blood flow and MVO_2 in our two groups of patients after eliminating this variable.

In addition to the effects of changing arterial pressure, an analysis of the reliability and sensitivity of several other techniques used in this study is in order. Left ventricular cineangiography has been shown to be a reliable method of determining left ventricular volume (30). The basic assumption, however, is that the shape of the ventricle is inellipsoid of revolution and deviations from this may introduce error. Since each patient was used as his own control and the extent of wall motion abnormality was similar on both angiograms, errors in the estimation of left ventricular volume, if present, would tend to cancel out.

Maintenance of the steady state for the period of time required to complete the study and the use of angiography early in the procedure both place a limitation

on the study and for this reason the control group was required. Angiographic contrast material is known to produce transient depression of left ventricular function (9). The ½-h waiting period which was inserted into the procedure was shown to be adequate to allow return of left ventricular end-diastolic pressure, cardiac output, heart rate, and arterial pressure to base-line values before ouabain administration.

The use of Xenon 133 technique for the estimation of coronary blood flow requires homogeneity in the distribution of flow, a prerequisite which is not met in the normal heart and certainly not in patients with coronary artery disease (31). Klocke et al. (32) have shown that the technique tends to overestimate flow, presumably because the coronary sinus effluent more closely reflects the areas of myocardium which are better perfused.

The measurement of coronary blood flow could also be affected by changes in the distribution of flow after an intervention because this would produce a change in the degree of homogeneity. Previous studies, however, have suggested that digitalis glycosides do not produce a change in the distribution of coronary blood flow (33). However, despite acknowledged inaccuracies in the absolute measurements we feel this technique provides meaningful data regarding the magnitude and direction of changes in coronary blood flow. There is no completely satisfactory technique for the estimation of coronary blood flow in man.

The determination of lactate extraction by simultaneous arterial and coronary sinus sampling gives values which represent the average for the myocardium. Though the average extraction may not change, regional areas of metabolic deterioration may be compensated by improved metabolism elsewhere in the heart. This could be detected only by regional sampling. Similarly total coronary blood flow may increase even though it may not change in some areas because of fixed obstruction of coronary lumina. Therefore, care should be exercised in applying our data to regional circulation.

The systemic and probably coronary vascular resistance as well can be modified by a direct effect of ouabain on arterial smooth muscle (4, 34). Preliminary data from our laboratory show that the metabolic and hemodynamic effects produced by ouabain are also dependent upon the rate of infusion of the drug (35). This effect on the peripheral bed can be avoided simply by prolonging the duration of the infusion to 15 min (35) as we have done in this study. Because progressively greater changes in afterload occur as the rate of infusion is increased, different effects on coronary flow and myocardial oxygen needs might have occurred if ouabain were given rapidly.

CONCLUSIONS

We conclude that left ventricular end-diastolic pressure and end-diastolic volume fell even though both were initially normal. Ouabain increased MVO_2 by increasing the contractile state of the myocardium but this effect was partially or completely counter-balanced by the decrease in left ventricular volume. Myocardial metabolism did not deteriorate suggesting that any increase in oxygen demand was met by beneficial changes such as increased coronary blood flow or oxygen extraction.

Care is required in extrapolating the results obtained in this study of resting patients with chronic coronary artery disease and without clinical congestive heart failure to patients with either acute myocardial infarction or congestive heart failure, or to the patient stressed by exercise or by increased afterload because the effects of ouabain may be either more favorable or less favorable in these states.

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